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ABSTRACT

The evidence for the claim that the autonomic innervation apparatus consists of a syncytial nerve net or a nerve cell net (network of 'interstitial cells') has been critically examined from morphological and physiological points of view. It is concluded that both the arguments and the cytological, neurohistological and physiological observations presented by earlier workers in this field, especially by BOEKE, LEEUWE, MEYLING and JABONERO, are open to severe objections. Further, it is shown that available morphological evidence strongly speak against their views on the innervation of autonomic effectors. The concept of the 'autonomic groundplexus' (HILLARP 1946) as being the innervation apparatus is discussed and considered to give a more adequate explanation of morphological as well as physiological observations. The fundamental phenomena of spatial and temporal summation in autonomic neuroeffector systems are regarded to be explained more adequately by this concept than by the transmitter diffusion theory of CANNON-ROSENBLUETH.

It has been claimed by several neurohistologists that the autonomic innervation apparatus has a syncytial construction. The innervation is considered to take place by means of a network of neurofibrils (the 'terminal reticulum' of STÖHR) or of nerve cells (the 'interstitial cells' of BOEKE, LEEUWE and MEYLING). This paper is concerned mainly with a critical analysis of the morphological and physiological evidence forming the basis of the above mentioned assumptions and, secondly, with a concept of the autonomic innervation providing a more adequate explanation of morphological and physiological observations.

MATERIAL AND METHODS

Neurohistological methods – For staining of the autonomic nerves the methylene blue method of SCHABADASCH (1935) was used with the modifications and precautions described in detail previously (HILLARP 1946). The uterus and iris of young rats were mainly examined.

NISSL substance was stained with gallocyanin-chromalun according to EINARSON (1932). Intestine, uterus and iris (rat, rabbit, cat)

were fixed in CARNOY's solution or in 95 per cent alcohol and embedded in paraffin.

The protagon granules of REICH in the intestines and various peripheral nerves from rabbit, cat and dog were demonstrated by the technique described in ROMEIS (1948).

Oxidase and peroxidase reaction – The methods of WINKLER-SCHULZE and FISCHEL-KREIBICH as described in ROMEIS (1948) were used on rabbit intestine. They were chosen to permit comparison with the results of LEEUWE (1937).

Sympathetic denervation of the eye – The cervical sympathetic trunk including the cranial cervical ganglion was extirpated down to the subclavian artery on one side (20 rats). The innervation of the iris was examined 7 to 14 days after the operation using the non-denervated iris as a control.

RESULTS AND DISCUSSION

I. THE INTERSTITIAL CELLS

On the basis of the studies made by LEEUWE (1937), MEYLING (1938) and BOEKE (1940, 1942, 1943) the interstitial cells of CAJAL have recently occupied a central position in conceptions of the autonomic innervation apparatus (NELEMANS and NAUTA 1946; NELEMANS 1948; JABONERO 1952, 1953, 1954; MEYLING 1948, 1953, 1954). Despite the highly speculative character of the new ideas in this field it seems necessary to pass some critical comment on the evidence claimed to prove the existence of a third neuron link in the peripheral autonomic innervation, since the views on this subject bear directly on the physiology and pharmacology of autonomic effectors (cf. AMBACHE 1947; FOLKOW 1955). Several neurohistologists, especially MEYLING (1938, 1948, 1953, 1954) and JABONERO (1952, 1953), claim that the interstitial cells – previously usually interpreted as sheath cells enclosing the terminal postganglionic axon ramifications – are true nerve cells and constitute the actual innervation apparatus. According to their interpretations, the groundplexus of BOEKE is built entirely of syncytially connected nerve cells providing a closed network on which the postganglionic fibres, sympathetic as well as parasympathetic,

make synaptic contacts. This network is claimed to be exclusively adrenergic and to possess many peculiar properties, but it is necessary to consult the original articles in order to get an understanding of the character of the investigations. The essential point, however, is whether there really exists a peripheral network of *nerve cells*. The evidence brought forth for this view, mainly by LEEUWE (1937) and MEYLING (1938, 1948) has been accepted by BOEKE (1943, 1949), for instance, without any closer examination of its validity.

The nerve cell nature of the interstitial cells is claimed by LEEUWE (1937), BOEKE (1943, 1949), MEYLING (1938, 1948) and JABONERO (1953) to have been shown on the basis of the following observations and arguments. The cells have the same cytological characteristics as nerve cells: they are vitally stained by methylene blue, they contain NISSL substance and neurofibrils but, unlike the SCHWANN cells, no protagon granules and show positive oxidase and peroxidase reactions. Finally, the interstitial cells remain intact when the postganglionic fibres degenerate after transection. The evidence brought forth will be examined in detail below.

The cytology of the interstitial cells

The interstitial cells are easily recognized in neurohistological preparations showing their characteristic arrangement in the nervous endnet and the nerve fibres in them (see e. g. illustrations in SCHABADASCH 1934, 1935 and Fig. 10 in the present work). If these criteria are not fulfilled they cannot be identified with any degree of certainty. It is therefore difficult to decide whether the interstitial cells reproduced by LEEUWE (1937) and MEYLING (1938) really are such cells and not clasmatocytes, for instance, as suggested by STÖHR (1957). This difficulty is well illustrated by the fact that even JABONERO (1952–1953), who supports his view concerning the interstitial cells on the studies of MEYLING, does not consider certain cells described by MEYLING (1938) as interstitial cells to belong to this category. The uncertainty of their identification is well documented in the neurohistological literature (cf. STÖHR 1954–55; CLARA 1954–55). In our laboratory the interstitial

cells have been studied for years and it is quite clear that they can only be identified in microscopical specimens prepared by special neurohistological methods (such as methylene blue staining and silver impregnation) but not in preparations made with common histological and cytological methods. Thus, for instance, when using various methods for staining of NISSL substance or for histochemical demonstration of oxidases and peroxidases it is not possible to identify the interstitial cells. This alone is enough to question the tenability of the statements of LEEUWE, MEYLING and others (see below) on the cytology of these cells.

OKAMURA (1934), LEEUWE (1937), MEYLING (1938, 1948), LI (1940) and SPOERRI (1949) claim to have shown the presence of NISSL substance in the interstitial cells. Previously (HILLARP 1946) and in the present investigation extensive material from frog, rat, rabbit and cat was used in order to check their observations. To secure optimal conditions for examination of the cells, sections were prepared parallel to the flattened smooth muscle layers of the intestine, uterus and iris where the interstitial cells form a dense network. But even then the cells could not be identified and no basophilic structures were seen that might be thought to belong to the interstitial cells. The drawings published by LEEUWE (1937), MEYLING (1938) and BOEKE (1943) are not convincing, an assertion strengthened by the fact that the supposed NISSL bodies were found (LEEUWE 1937) to give the FEULGEN reaction. But even if the above mentioned authors had seen some basophilic structures in the interstitial cells, it would not forthwith imply the presence of NISSL granules. The tests applied by LEEUWE (1937) to identify the granules do not need commentation.

LEEUWE (1937) claims that the interstitial cells have histochemically demonstrable oxidases and peroxidases. Though this could not be confirmed in our material using the same methods as LEEUWE and though the drawing in his paper is by no means convincing as regards the identity of the cell, it is possible that the interstitial cells may give these reactions. But the often repeated statement of MEYLING, BOEKE and JABONERO that this is evidence for the nerve cell nature of the interstitial cells cannot be accepted, since several other cell types, including neuroglia cells (BIELSCHOWSKY 1935), also show the oxidase reaction. Further-

more, it may be the axons in the interstitial cells that give the reactions.

The uncritical attitude of BOEKE, MEYLING, LEEUWE and JABONERO towards cytological problems is further illustrated by their argument that the absence of protagon granules in the interstitial cells shows that they are not neurilemma cells. As a matter of fact, these granules can usually only be found in somatic nerve fibres and they do not occur in peripheral nerves in several animals (ROBSON 1951; NOBACK 1953). As far as is known, they are not present in the neurilemma cells of the postganglionic nerve fibres. This has been confirmed in the present work using material from rabbits, cats and dogs.

The fact that the interstitial cells may be stained "supravitally" with methylene blue is considered as strong evidence for their being of nervous nature. This staining must therefore be dealt with in some detail. Experience with the methylene blue technique of SCHABADASCH, which in essential respects (cf. HILLARP 1946) is superior to other neurohistological methods, has been obtained at our laboratory by its use for more than eight years. Under certain conditions (found by varying pH, concentration of methylene blue and other substances in the staining solutions, injection and developing time etc.) this method may be standardized to give a specific staining of the axons of peripheral nerve fibres, specific in the sense that no non-nervous fibrillar structures take the stain.[1] The neurilemma cells and nerve cells are completely unstained but the interstitial cells may show a faint blue staining. Figs. 3, 4 and 8–10 show autonomic nerves as demonstrated by this "pure" staining. In a previous work (HILLARP 1946) this modification of the method was predominantly used because it gives the best picture of the autonomic innervation and because the method – in contrast to all other methods – is specific in the sense stated above. Using other conditions (such as higher pH, higher concentration of methylene blue and longer developing time) the cytoplasm of the interstitial cells may show a diffuse or granular staining of varying intensity obscuring the axons (Figs.

[1] Although the term "specific" was celarly defined in this way, this has often not been recognized (see e. g. STÖHR 1954–55).

6 and 7). Even the neurilemma cells of the preterminal nerve plexuses may be similarly stained (Fig. 5). The nuclei of the interstitial cells may or may not stain under the same conditions. The nerve cells bodies in the intramural autonomic ganglia are often completely unstained when the interstitial cells show a marked staining. Demonstration of the nerve cells usually requires a high methylene blue concentration and a long developing time. As known, many other cells may be stained with methylene blue. It is thus obvious that the methylene blue staining cannot be interpreted as a "biologische Reaktion des Neuroplasma" as thought by LEEUWE and MEYLING.

BOEKE, LEEUWE, MEYLING and JABONERO repeatedly state that the fibres seen in the interstitial cells are neurofibrils and not axons. As a matter of fact, however, no acceptable evidence for this view has ever been presented. The following facts and arguments strongly support the opposite view.

1. The fibres running in the autonomic endnet have a very peculiar morphology indicating their axonic nature. These fibres with their varicosities, round or elongated enlargements, often lying close to each other look like strings of beads. The varicosities are best seen in preparations obtained with the "pure" methylene blue staining referred to above (Figs. 4 and 8–10) but are often observed also after silver impregnation (see e. g. Figs. 23, 24, 26 and 27 in BOEKE 1940). Varicosities are never found on neurofibrils within axons or nerve cell bodies. On the other hand, they are quite typical of terminal autonomic axons. They are thus present on the preganglionic axon ramifications in the autonomic ganglia (see illustrations in HILLARP 1946) and are also common on axons running in the preterminal postganglionic plexuses (Fig. 4).

2. In methylene blue preparations it is possible to observe how the postganglionic nerves running to an organ (Fig. 1) form intramural plexuses of nerve fibre bundles (Fig. 2). From the preterminal bundles the axons then enter[2] the terminal network of anastomosing interstitial cells to run in their cytoplasm as highly vari-

[2] This has repeatedly been observed and described also by STÖHR, BOEKE, SCHABADASCH and others.

cose and extremely fine fibres. The fibres in the endnet are thus continuous with the preterminal axons and differ from the latter only by being thinner and more varicose. The only reasonable conclusion is that the fibres in the interstitial cells are postganglionic terminal axon ramifications. The postganglionic axons run in the SCHWANN plasmodium of the peripheral nerves and intramural plexuses the whole way out to the effectors, finally to radiate into the endnet, and there is no reason to believe that their axoplasm should be lost or merge into the cytoplasm of the interstitial cells.

3. The fact that the fibres in the interstitial cells degenerate after division of the postganglionic nerves (see below) strongly supports the view that they are terminal axon ramifications from the postganglionic fibres.

4. Finally, electron microscope observations (CAESAR, EDWARDS and RUSKA 1957) seem to show that the terminal autonomic nerve fibres are axons, surrounded by accompanying sheath cells.

Degeneration of the nerve fibres in the interstitial cells after division of the postganglionic nerves

The final and crucial claim that the nerve fibres in the interstitial cells do not degenerate after division of the postganglionic nerves is not supported by evidence hitherto available. It is meaningless to discuss most of the studies (LAWRENTJEW 1934; REISER 1937, 1938; STÖHR 1934, 1941; WEDDELL, HARPMAN, LAMBLEY and YOUNG 1940) to which MEYLING and JABONERO have referred because these studies obviously have no bearing on the problem. The contribution made by MEYLING (1938) is a report that interstitial cells were observed in the *carotid sinus* of a horse 25 days after the transection of the sinus nerve and the nerves between the external and the internal carotid arteries. Even if the cells described by MEYLING were interstitial cells, which is questionable (see below), there is certainly no guarantee that the tissue examined had been deprived of all its autonomic nerves. This also holds for NELEMANS' (1948) finding of an apparently normal network of interstitial cells in the frog's tongue after divi-

sion of the glossopharyngeal and hypoglossal nerves. Contrary to this NELEMANS in a later work (NELEMANS and DOGTEROM 1954) found the autonomic endnet in the eye and ear of the rat to undergo a rapid degeneration on division of all the postganglionic nerves.

That the nerve fibres in the autonomic endnet degenerate after section of the nerves going to it has previously been demonstrated in the submaxillary gland (GLIMSTEDT and HILLARP 1942) and in the pars intermedia of the pituitary (HILLARP and JACOBSOHN 1943). In the present work the iris innervation was studied. With the method used the fine varicose fibres running in the endnet enclosing the smooth muscle layer of the small vessels showed up distinctly. After sympathectomy these fibres completely disappeared though anastomosing interstitial cells were now and then faintly visible. The most reasonable explanation is that the fibres in the endnet innervating the small iris vessels degenerate on account of their being sympathetic postganglionic axon ramifications.[3] There is no needs to go into details as SZENTÁGOTHAI (1957) recently more directly has demonstrated the degeneration of the nerve fibres in the autonomic innervation apparatus.

Nature of the interstitial cells

The view that the interstitial cells are nerve cells is founded mainly on the works of LEEUWE (1937) and MEYLING (1938). From the considerations presented above it seems clear that the *conclusions* made on the basis of their cytological studies cannot be accepted. Objections may also be raised against their investigations as such, however. The main objection is that it is questionable whether the cells studied by them really are interstitial cells.

The interstitial cells – as observed in methylene blue preparations – form a network of anastomosing, *rather slender protoplasmic strands with smooth and distinct outlines.* Excellent microphotographs showing their appearance have been published by

[3] The abundant nerve supply to the other parts of the iris was apparently not affected by sympathectomy. This is easily explained by the fact that the iris has a predominantly parasympathetic innervation.

Schabadasch (1934, 1935). A study of the cells in the drawings made by Leeuwe and Meyling show quite clearly that none of the cells have this characteristic morphology and that many have a totally different appearance. Furthermore, the faint and indistinct "neurofibrils" in the cells bear no resemblance to the varicose nerve fibres that may easily be demonstrated in the interstitial cells by both methylene blue and silver impregnation methods.

It may be concluded that it is not possible to accept the arguments or the cytological and neurohistological evidence presented in support of the view that a terminal syncytium of nerve cells is interposed as an innervation structure between the postganglionic neurons and the autonomic effector cells. There is thus no reason to suppose that the interstitial cells are anything but neurilemma cells, as suggested long ago by Lawrentjew, Stöhr, de Castro, Schabadasch, Nageotte and others. This is the most reasonable explanation, since the nerve fibres in the terminal network must be regarded as fine postganglionic axon ramifications supplied from the small preterminal nerve bundles which are continuous with the endnet. This concept has recently been strongly supported by careful studies by Greving and Berg (1954), Greving and Dressler (1954), Herzog (1954) and Szentágothai (1957).

II. THE SYNCYTIAL NERVE NET HYPOTHESIS FROM PHYSIOLOGICAL POINTS OF VIEW

It is now and then suggested (see e. g. van Esveld 1928; Fischer 1944; Ambache 1947) that certain physiological and pharmacological properties of smooth muscle are best explained on the basis of a nervous terminal syncytium. The propagated conduction in various visceral muscles and the diffuse character of the responses obtained on stimulation of only a small fraction of the nerves supplying a smooth muscle might be interpreted as speaking in favour of this view. Strictly localized responses have been clearly demonstrated in several smooth muscles (Langley 1904; Hofmann 1904; Elliott 1905; Anderson 1905–06; Gilding 1932; Morison 1940; Lutz, Fulton and Akers 1950; Downman 1952),

however, and the diffuse responses usually obtained were adequately explained by LANGLEY (1904) as being due to "the intermingling of the postganglionic fibres which occurs in the preterminal plexus on the way to the tissues". Furthermore, the view that conduction in smooth muscles takes place in a synaptic or asynaptic nerve net has been severely criticized on the basis of the finding that conduction is not inhibited by local anaesthetics (BOZLER 1938; FELDBERG and LIN 1949; BÜLBRING 1955; SLEATOR and BUTCHER 1955) or by ganglion blocking agents (FELDBERG 1951; SCHOFIELD 1952; BÜLBRING 1955; EDGE 1955) and there is good evidence that conduction is of a myogenic nature (for references see HILLARP 1959).

The syncytial nerve net theory introduces many difficulties and hardly seems compatible with some important experimental results. In an attempt to explain locally restricted responses it is postulated that the impulse conduction in the assumed nerve net takes place with a decrement (FISCHER 1944; SCHAEFER 1952), but, on the other hand, this nerve net is adopted to explain propagated conduction, too (see e. g. FISCHER 1944). There is good evidence that in some effectors *one and the same group of cells* is innervated by two sets of fibres with antagonistic actions, in some instances shown to be adrenergic and cholinergic, respectively. An innervation of this type has been demonstrated for the pacemaker of the heart (ROSENBLUETH and SIMEONE 1934), the cat's retractor penis (OPPENHEIMER 1938), some small blood vessels (LUTZ, FULTON and AKERS 1950), the cat's submaxillary and sublingual glands (EMMELIN 1955; LUNDBERG 1955, 1957) and for the melanophores of fishes (PARKER and ROSENBLUETH 1941) and is probably present in other effectors supplied by antagonistic nerves. The postulate of a nerve cell syncytium or of a nerve net in which all efferent fibres are syncytially connected seems to be incompatible with the conception of a dual innervation.

Further, the assumption that the terminal parts of the autonomic innervation structure may remain more or less intact after degenerative transection of the postganglionic nerves – a correlate to the syncytium theory – is hardly in accord with the evidence presented by VON EULER and his associates (VON EULER 1951, 1956, 1957, 1958; VON EULER and PURKHOLD 1951; GOODALL

1951) strongly indicating that the adrenergic transmitter is accumulated in the nerve terminals and clearly showing that it disappears on degeneration of the postganglionic fibres.

Finally, it seems hardly possible to give a reasonable explanation to the classical experiments of CANNON and ROSENBLUETH on temporal and spatial summations in autonomic neuro-effector systems (see Section III) on the basis of a nerve cell net or a syncytial nerve net.

III. THE CONSTRUCTION OF THE AUTONOMIC INNERVATION APPARATUS

MORPHOLOGICAL POINTS OF VIEW

The neurohistological investigations of the last twenty years have given rise to many divergent opinions on the construction of the autonomic innervation apparatus. There are two factors mainly responsible for this confusion; unreliable histological methods and a general tendency not to use rigid criteria for interpretation of the microscopically observable structures. The nonspecificity of silver impregnations is well-known and it has been clearly shown that the fixation procedure and other treatments of the tissues by these methods give rise to serious artefacts (LAWRENTJEW 1926; HOERR 1936; HILLARP 1946; WEDDELL and ZANDER 1951; HERZOG 1954; KIRSCHE 1954, 1955). Nevertheless, many prominent neurohistologists, such as STÖHR, BOEKE, and their students (see e. g. BOEKE 1940; STÖHR 1941) claim that the peripheral extensions of the autonomic nerve fibres have a syncytial construction and a continuous neurofibrillar connection with a network located within the innervated cells, a network with fibrils of such fine dimensions as to border the limit for the resolving power of the microscope. It is obvious that the claims made by STÖHR and BOEKE cannot be accepted until very strong evidence has been furnished that the structures demonstrated are of nervous nature and existent in the living tissues. No such evidence has as yet been presented, however, in earlier (cf. HILLARP 1946) or recent papers (BOEKE 1949; REISER 1952; STÖHR 1950, 1954,

1957). Furthermore, their descriptions to the microscopical appearance of the nervous syncytia are quite different and partly incompatible in spite of the fact that both STÖHR and BOEKE use silver impregnations and that they both argue along the same lines on the validity of their views. This gives a good illustration of the difficulties inherent in their methods. A detailed criticism of their neurohistological studies has been published (HILLARP 1946). How unreliable silver impregnation may be, is seen from a comparison between the views of BOEKE on the construction of the motor end-plate and its structure as revealed by the electron microscope (see e. g. ROBERTSON 1956).

Up to 1932 the autonomic effector cells were considered to have principally the same type of individual innervation as voluntary muscle, the postganglionic fibre terminating in an extra- or intracellular nerve ending. This view was radically changed by the introduction of STÖHR's 'terminal reticulum' and BOEKE's 'sympathetic groundplexus', demonstrating far more extensive nerve structures than were previously anticipated. The terminal reticulum is built up of continuously anastomosing neurofibrillar elements emerging from the finer nerve plexuses and forming a syncytially constructed network woven in between all kinds of cells, connective tissue cells as well as true effector cells. Both the sympathetic and the parasympathetic fibres pass into this gigantic syncytium partly embedded in the cytoplasm of the innervated cells. The sympathetic groundplexus is a fine-meshed network of anastomosing protoplasmic strands with interspersed SCHWANN cell nuclei and containing extensively anastomosing neurofibrils. The strands are connected in their proximal part to coarser nerve fibres and distally they are in protoplasmatic continuity with a system of interstitial cells, interpreted to be nerve cells and to form "the endformation which brings the effector cells into contact with this nervous groundplexus; they are an intrinsic part of it; they form the synaptic part of the endformation . . ." (BOEKE 1949). The statements of BOEKE on this point are somewhat confusing and the construction is rather unconventional with the sheath cells of SCHWANN in direct continuity with nerve cells. Still more confusing is the existence of a 'periterminal network' in the innervated cells which is claimed to be connected to the

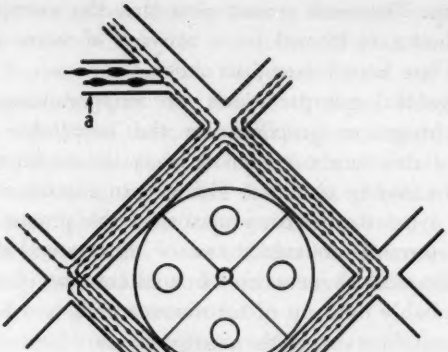
groundplexus. The more recent view that the autonomic innervation apparatus is formed by a network of nerve cells (interstitial cells) has been referred to above.

If all doubtful interpretations are stripped away from the various constructions proposed for the autonomic innervation apparatus, a structure common to many or maybe most of the constructions may be obtained. This structure is the essential part of BOEKE's sympathetic groundplexus, of the proximal extension of STÖHR's terminal reticulum and of the system of interstitial cells: a fine-meshed network of anastomosing protoplasmatic strands, probably built up of neurilemma cells (see Section I), in which the ramifications of the postganglionic fibres are taken up. By means of a neurohistological technique less open to objections than the commonly used silver impregnation the morphological construction of this structure (in the following called autonomic groundplexus) and its relations to the postganglionic fibres and the effector cells have been extensively studied in glands and smooth muscles (HILLARP 1946).

Figs. 6 and 7 are microphotographs of the groundplexus where the anastomosing protoplasmatic strands are stained so that the axons running in them are not clearly visible. In Figs. 8 to 10 the nerve fibres in the groundplexus are stained but not the protoplasmatic strands. It is seen that usually several varicose axons run together in the same strand. A schematic drawing of the construction of the groundplexus is given in Textfig. 1.

Disregarding the periterminal network, the real existence of which never has been shown, the fundamental differences between the observed autonomic groundplexus and the corresponding plexus of BOEKE are that the fibres embedded in the protoplasmatic strand do not show extensive syncytial connections and that they must be interpreted as very fine terminal axons and not neurofibrils, as claimed by BOEKE (see Section I). It has been shown in Section I that there is good evidence that the cells (interstitial cells) forming the terminal network are sheath cells (neurilemma or SCHWANN cells) and not nerve cells.

The neurohistological investigation referred to above led to a new concept of the innervation of autonomic effectors, according to which the innervation takes place by means of the autono-



Textfigure 1. Schematic representation of the autonomic groundplexus, based on observations of the morphology of the groundplexus and on evidence from experimental studies (see text). The groundplexus is built of a three dimensional network of sheath cells, a mesh of which is shown (surrounding a glandular end-piece). Axons from the preterminal nerve bundles (a) enter the groundplexus (b), whose strands contain several axons derived from different neurons. There is thus a convergence of nerve terminals from different neurons to one effector cell group. Since the groundplexus is directly superimposed on the effector cells (not shown in figure), the chemical mediator liberated from the axons has a very short distance to diffuse to reach the cells.

mic groundplexus: a plexus of axon ramifications embedded in a fine-meshed network of anastomosing strands formed by the terminal SCHWANN plasmodium and directly superimposed on and probably contacting all effector cells. The view that the plexus is the real innervation structure is partly hypothetical, since it is based on the assumption that the plexus is a closed terminal formation. But the construction of the plexus regarded as a whole strongly supports this concept (cf. HILLARP 1946).

PHYSIOLOGICAL POINTS OF VIEW

The morphological construction of the autonomic groundplexus does not in itself give any clue to the functional organization of the effector innervation. CANNON, ROSENBLUETH and their associates (cf. ROSENBLUETH 1932; ROSENBLUETH and RIOCH 1933; ROSENBLUETH and MORISON 1934; CANNON and ROSENBLUETH 1937) made the basic experiments necessary for an understanding of this organization more than twenty years ago, and they formed a theory providing a logical explanation for the phenomena observed. This theory is founded on the assumption that only some of the effector cells are directly innervated. The chemical mediator liberated by the nerve impulses in or at these 'key cells' diffuses to the non-innervated cells and this free diffusion explains their fundamental observation that spatial and temporal summation are quantitatively interchangeable in autonomic effectors, the response being dependent of the number of impulses per unit time only and not on the number of activated nerve fibres. In contrast to voluntary muscle, autonomic neuro-effector systems are thus not organized in units, but the innervation is quite diffuse. Now, it is obvious that the key cell principle is no necessary part of the theory and may be dropped, as it apparently has been by ROSENBLUETH (1950). Of essential importance are the theoretic aspects on the liberation, diffusion and action of the mediator. Much evidence has accumulated in favour of the CANNON-ROSENBLUETH theory (cf. ROSENBLUETH 1950) and certainly any new theory concerning the innervation of autonomic effectors should account for the phenomena of spatial and temporal summation in the effectors.

Although leakage of the adrenergic mediator to the blood and a diffusion within autonomic effectors have been demonstrated, this diffusion may not have any physiological significance in the innervation of an effector system. Direct evidence concerning this problem has been obtained from studies of the cytologically registrable cell reactions evoked by reflex stimulation of the nervous centers of the adrenal medulla (HILLARP 1946) and the submaxillary gland (HILLARP 1949) with innervation intact or partially denervated. Space will not permit more than a brief sum-

mary, but a detailed discussion of the validity of the conclusions is found in the original papers. Both in the cholinergic systems and in the adrenergic system examined in the experiments the results speak for the view that the cell complexes are organized in units which may be submaximally stimulated or drop out of activity altogether on partial denervation of the glands. The presence of more or less submaximally activated complexes in spite of intense stimulation producing exhaustion changes in cells with intact innervation, indicates that each unit receives nerve terminals from several neurons. The results also speak strongly against the assumption that a transmitter diffusion is an important innervation mechanism. For instance, denervated cell complexes do not show any activation through mediator diffusion from highly active complexes immediately adjacent to the denervated ones in spite of prolonged, intense stimulation, denervation supersensitivity and cholinesterase inactivation. These results are obviously inconsistent with the transmitter diffusion theory of CANNON-ROSENBLUETH. However, it is possible to form a new concept of autonomic innervation which may give an alternative explanation for the observations of temporal and spatial summation in autonomic effector systems as well as for some of ROSENBLUETH's observations not accounted for in his theory. This concept, which also gives a reasonable explanation of the puzzling morphological construction of the innervation structure, especially the existence of several axons in each strand of the plexus, may be briefly summarized as follows:

The innervation structure consists of the autonomic groundplexus within which each terminal axon ramification has a certain extension and in its course innervates a certain number of cells or cell complexes forming a neuro-effector unit. To each unit, however, several postganglionic neurons converge, the terminal axon ramifications of which run within the same strands of the ground plexus (Textfig. 1). By the overlap thus present in the innervation structure the response of the effector system may be modified by both temporal and spatial summation.

It is obvious that this concept in no way contradicts CANNON-ROSENBLUETH's arguments or theories concerning the liberation and action of the chemical mediator. The mediator diffusion prin-

ciple is replaced by a convergence principle on the basis of which several experimental results inconsistent with the diffusion theory may have a logical explanation. As the discrepancies have not been pointed out by ROSENBLUETH, some of them will be briefly discussed.

From the crucial experiments on temporal and spatial summation in the nictitating membrane made by ROSENBLUETH and RIOCH (1933) it is clearly seen that, according to the diffusion theory, the mediator, liberated locally on stimulation of large or small fractions of the nerves, must be assumed to have a free diffusion to remote cells which is as complete and of the same effective magnitude when large or very small quantities are diffusing and when the diffusion distance is long or short. This seems quite unreasonable. The convergence principle, on the other hand, gives an adequate explanation for the experimental data: the spatial relationship between the site of release and the site of action of the mediator does not change when only a fraction of the nerves instead of all are stimulated. It can be seen from the same experiments that the mediator locally liberated by impulses in only a fraction of the nerves to the nictitating membrane must, according to the diffusion theory, be assumed to diffuse freely to all the muscle cells even at the lowest stimulation frequencies (< 1/sec). The results obtained in exactly the same type of experiments with chronic partial denervation of the membrane (KLOPP 1940) are quite inconsistent with this view and do not indicate a mediator diffusion until a relatively high stimulation frequency is used. Finally, ROSENBLUETH and RIOCH (1933) have shown that cholinergic systems also behave in the same manner as adrenergic with regard to temporal and spatial summation. This largely invalidates the whole diffusion theory. If it seemed unreasonable to assume the same free diffusion of the adrenergic transmitter under all the experimental conditions used, it certainly seems highly improbable to have such a diffusion mechanism in cholinergic effectors with their high power to destroy acetylcholine. — The view that there exists a considerable convergence of nerve terminals from different postganglionic neurons to one effector cell group is strongly supported by recent studies of the electrophysiology of the cat's submaxillary and sublingual glands (LUNDBERG 1955, 1957).

It might be argued that the mediator overflow found to occur on stimulation of adrenergic nerves speaks in favour of the view that there is a considerable transmitter diffusion within autonomic effectors, a diffusion which has even been considered to make the concept of innervation quite illusory. Though it is still too early to prove that the innervation theory suggested above holds for all effector systems, the existence of the same innervation structure in widely different effectors and the possibility of giving a more adequate explanation of the summation mechanism in cholinergic as well as in adrenergic systems, suggest a more general applicability of the theory. Furthermore, evidence is accumulating for the view that the adrenergic transmitters are to a large extent eliminated locally at the site of their release and that any significant accumulation and overflow do not take place on stimulation of adrenergic nerves with frequencies within the physiological discharge range (Folkow 1952; Celander and Folkow 1953; Celander 1954; Celander and Mellander 1955). Quantitative determination of the noradrenaline output from the spleen on stimulation at different frequencies strongly supports this view (Brown and Gillespie 1956).

There is good evidence that the chemical mediators are produced by and accumulated in the autonomic nerve terminals (cf. Rosenblueth 1950; von Euler 1951, 1956, 1957, 1958). All the available data also speak for the view of von Euler that the mediators are concentrated in high amounts in the terminals. In fact, the amounts are so large that it seems necessary to postulate that the individual endings, each constituting a transmitting junctional structure, cannot be tiny knobs or small axon expansions, but must have a considerable length. This is in good agreement with the assumption that the axon ramifications running in the autonomic groundplexus are true terminals releasing the transmitters when nervous impulses travel along them and thus acting on the effector cells with very short diffusion distances. This hypothesis makes it possible to explain the dual innervation of an effector cell without postulating the existence of two independent innervation structures, for which there is no morphological evidence. It does not seem unreasonable to suppose that axon terminals from both sympathetic and parasympathetic neurons may

be enclosed in the same groundplexus. On the contrary, all observations of the morphological construction of the plexus point in this direction. In this way both adrenergic and cholinergic mediators may be released from an innervation structure common to both autonomic systems.

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Figures 1 to 7 are micrographs and figures 8 to 10 are drawings (from HILLARP 1946) of preparations prepared by the methylene blue method of SCHABADASCH.

Fig. 1. Survey of the nerves and blood vessels reaching uterus. × 90.

Fig. 2. Survey of the nerve plexuses in stratum vasculare of uterus. × 90.

Fig. 3. Survey of the nerve plexuses in wall of left heart atrium. × 80.

Fig. 4. Preterminal nerve plexus in wall of left heart atrium. Only the axons are stained; the sheath cells are completely unstained. Some of the preterminal axons (at A) show varicosities. At B some very thin and highly varicose axons belonging to the autonomic groundplexus, only part of which is stained. × 600.

Fig. 5. Preterminal nerve plexus in uterine wall. In this case the sheath cell cytoplasm is predominantly stained; the axons are more or less unstained. × 480.

Fig. 6. Autonomic groundplexus enclosing a small branching blood vessel in stratum vasculare of uterus. The sheath cell cytoplasm is stained and masks the axons. × 520.

Fig. 7. Autonomic groundplexus in longitudinal muscle layer of uterus. The sheath cell cytoplasm is stained and masks the axons. The groundplexus is incompletely stained. × 540.

Fig. 8. Pars intermedia of the pituitary; rat. Autonomic groundplexus enclosing the cells in a gland lobe.

Fig. 9. Small muscle trabecula in the urinary bladder; frog. Autonomic groundplexus in the smooth musculature.

Fig. 10. Iris; rat. Autonomic groundplexus with stained Schwann cell nuclei (interstitial cells).

Fig. 1.

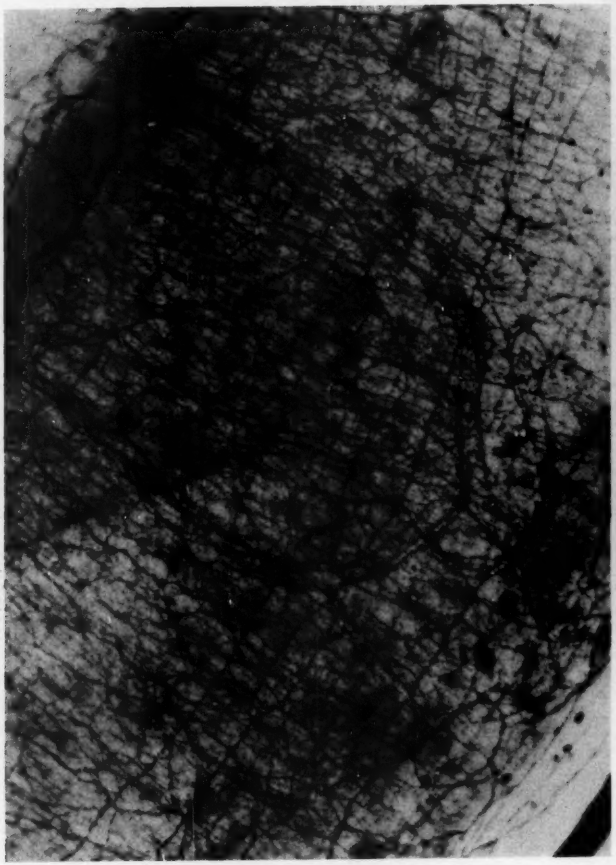


Fig. 2.

Fig. 3.

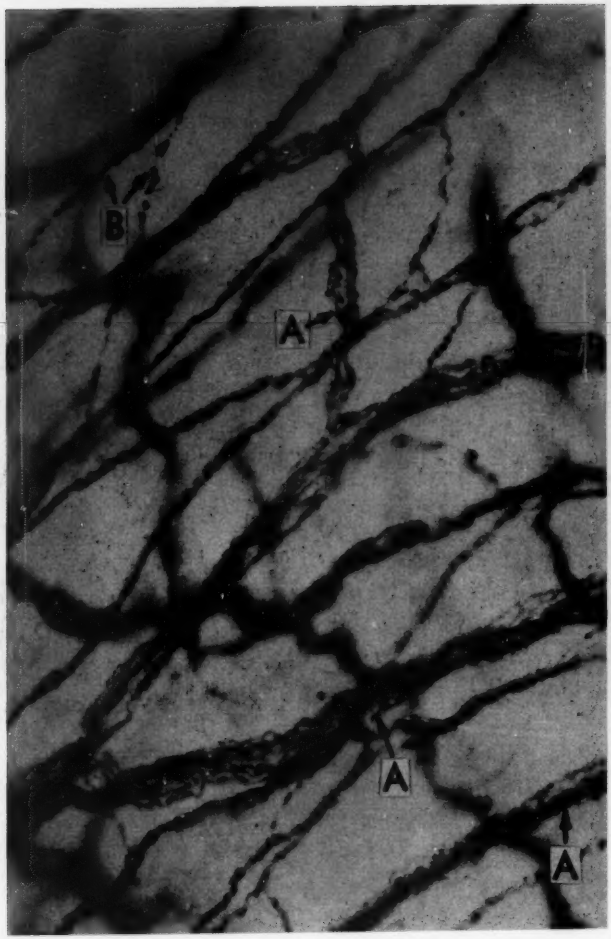


Fig. 4.

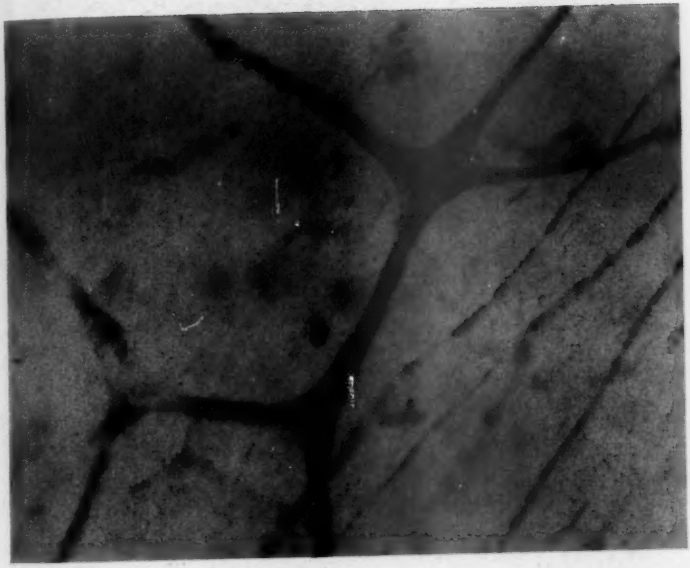


Fig. 5.

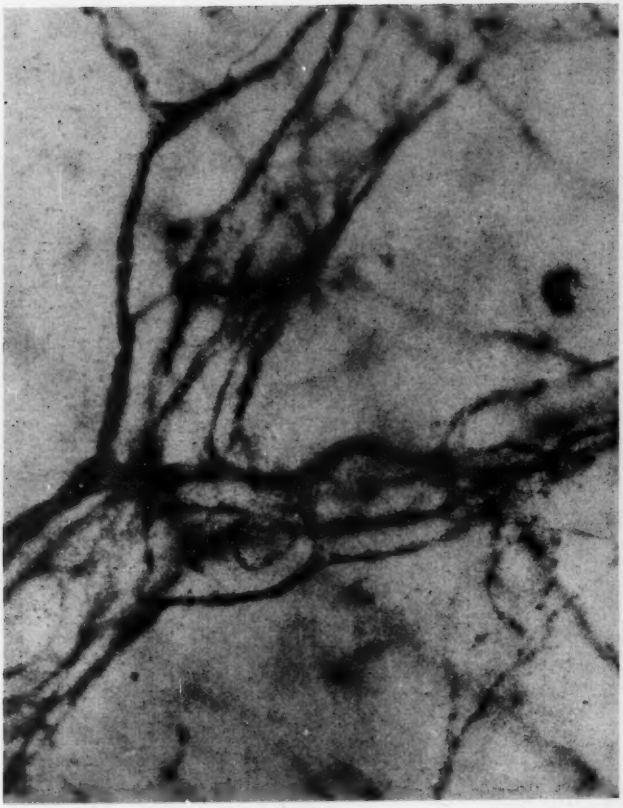


Fig. 6.

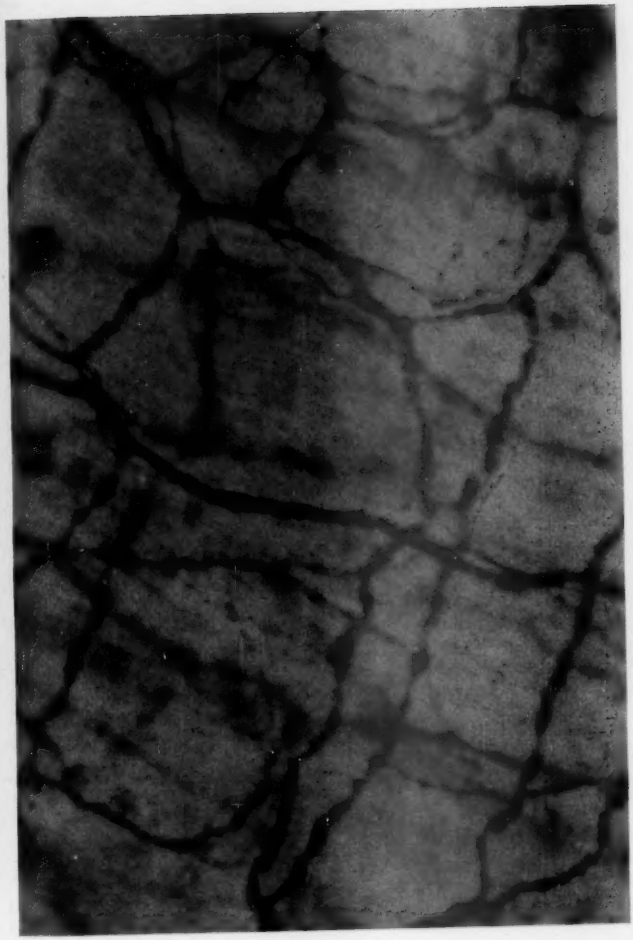
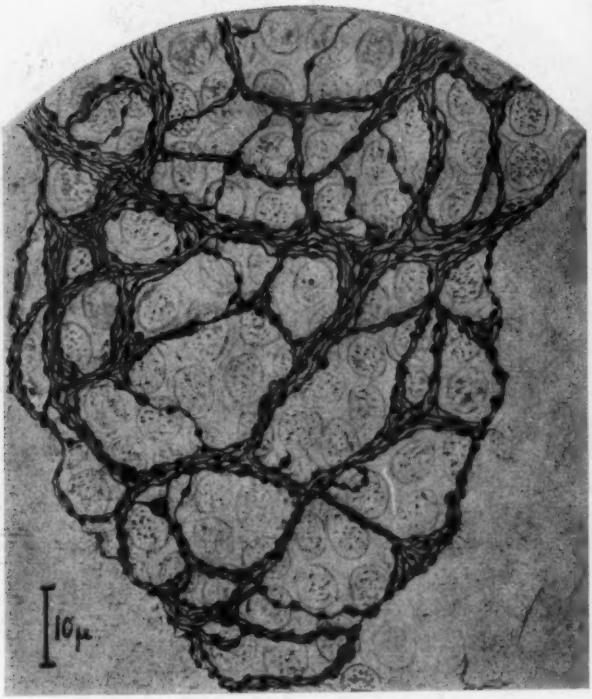


Fig. 7.



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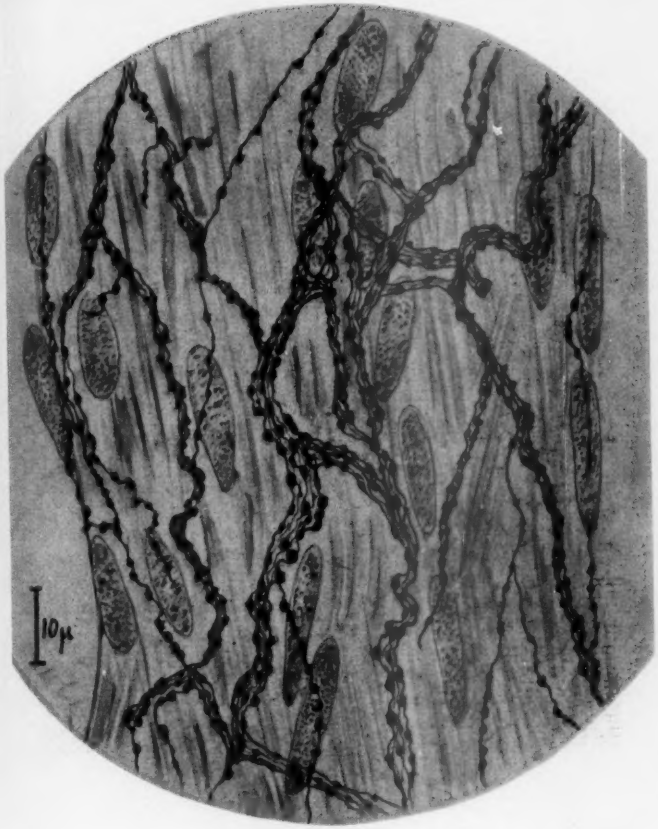

Fig. 9.

Fig. 10.

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